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- (71) Applicant (*for all designated States except US*): **MEDEVA EUROPE LIMITED** [GB/GB]; 208 Bath Road, Slough, Berks SL1 3WE (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **DAVIDSON, Elizabeth, Janina** [GB/GB]; Celltech Pharmaceuticals Limited, 208 Bath Road, Slough, Berks SL1 4EN (GB). **CRAIG, Fiona** [GB/GB]; 72 Auckland Road, Tunbridge Wells, Kent TN1 2HS (GB).
- (54) Agent: **GILL JENNINGS & EVERY**; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).
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(54) Title: THE TREATMENT OF CONVULSIVE STATES

(57) Abstract: Single enantiomer-*threo*-methylphenidate is useful in the therapy of a convulsant state, e.g. epilepsy, a bipolar disorder or narcolepsy. It may be administered topically.

INTERNATIONAL SEARCH REPORT

Int. Application No

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 27176 A (MEDEVA EUROP LTD) 31 July 1997 (1997-07-31) the whole document	1-6
A	ECKERMAN D A ET AL: "ENANTIOSELECTIVE BEHAVIORAL EFFECTS OF THREO-METHYLPHENIDATE IN RATS" PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR, ELSEVIER, US, vol. 40, no. 4, 1991, pages 875-880, XP000602558 ISSN: 0091-3057 the whole document	1-6

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Engl, B

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>AOYAMA T ET AL: "NONLINEAR KINETICS OF THREO-METHYLPHENIDATE ENANTIOMERS IN A PATIENT WITH NARCOLEPSY AND IN HEALTHY VOLUNTEERS" EUROPEAN JOURNAL OF CLINICAL PHARMACOLOGY, SPRINGER VERLAG, DE, vol. 44, no. 1, 1993, pages 79-84, XP000602466 ISSN: 0031-6970 the whole document</p>	1-6
A	<p>DING Y-S ET AL: "CHIRAL DRUGS: COMPARISON OF THE PHARMACOKINETICS OF 11CD-THREO AND I-THREO-METHYLPHENIDATE IN THE HUMAN AND BABOON BRAIN" PSYCHOPHARMACOLOGY, SPRINGER VERLAG, BERLIN, DE, vol. 131, 1997, pages 71-78, XP000964662 ISSN: 0033-3158 the whole document</p>	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9727176	A	31-07-1997	AU 716570 B2	02-03-2000
			AU 1450397 A	20-08-1997
			CA 2242595 A1	31-07-1997
			CZ 9802251 A3	16-12-1998
			EP 0883608 A1	16-12-1998
			WO 9727176 A1	31-07-1997
			HU 9900798 A2	28-07-1999
			JP 2000517288 T	26-12-2000
			SK 98098 A3	10-03-1999
			US 6242464 B1	05-06-2001
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(57) Abstract: Single enantiomer-*threo*-methylphenidate is useful in the therapy of a convulsant state, e.g. epilepsy, a bipolar disorder or narcolepsy. It may be administered topically.

THE TREATMENT OF CONVULSIVE STATESField of the Invention

This invention relates to the treatment of epilepsy and other convulsive states, bipolar disorder and narcolepsy.

Background of the Invention

Existing therapies for epilepsy have a variety of associated problems. For example, Epilim® (sodium valproate) is associated with liver dysfunction, including hepatic failure which has resulted in death, and has been found to interact with other drugs such as monoamine oxidase inhibitors. Drowsiness and sedation are among the side-effects on the CNS that have been noted for Epanutin® (phenytoin) and the benzodiazepine Valium® (diazepam). Drugs with the capacity to inhibit hepatic enzymes, such as cimetidine and omeprazole, have been found to reduce the clearance of benzodiazepines and can potentiate their action.

A further issue with existing anti-epilepsy treatments is patient compliance. Most of the oral treatments require repeated dosing within the day and it is not uncommon for doses to be omitted in error or inadvertently for logistical reasons.

Recent studies in humans have shown that anticonvulsant drugs have some efficacy in bipolar disorder (Scrip, No. 2484, October 22nd 1999). The principal existing treatment, lithium, has drawbacks. For example, it is effective in only 50% of patients, monitoring of blood levels is required, and its use causes side-effects which lead to low compliance.

d,l-threo-methylphenidate (*d,l*-MPH) is available as Ritalin®. The ABPI Compendium of Data Sheets and Summaries of Product Characteristics (1999-2000) states that "Ritalin should be used with caution in patients with epilepsy as clinical evidence has shown that it can cause an increase in seizure frequency in a small number of such patients". See also the US Physicians' Desk Reference.

Patrick et al, J. Pharm. Exp. Ther. 24:152-158 (1987), indicates that the pharmacological action of *d,l*-MPH in the treatment of attention-deficit hyperactivity disorder (ADHD) is the property of the *d*-enantiomer (*d*-MPH), as no
5 action on the part of the *l*-enantiomer (*l*-MPH) has been detected; see also Srinivas et al, Clin. Pharm. Ther. 52:561-8 (1992). It has also been found that, following oral dosing, the *l*-enantiomer is metabolised preferentially, such that plasma levels of the *d*-enantiomer
10 are generally found to be higher than those of the *l*-enantiomer (Aoyama et al, Eur. J. Clin. Pharm. 44:79-84 (1993); Hubbard et al, J. Pharm. Sci. 78:944-7 (1989)), and that very little *l*-MPH enters the circulation or becomes available to the brain.

15 Intravenous administration of *d,l*-MPH has shown similar plasma levels of the two enantiomers for around 1.5 hours after dosing, after which the levels diverge (Srinivas, Pharm. Res. 10:14-21 (1993)). Ding et al, Psychopharmacology 131:71-78 (1997), has shown that *l*-MPH
20 is detected in the brain after intravenous dosing.

WO-A-99/30694 discloses the topical application of *d,l*-MPH, using substantially zero order kinetics. An example of a topical composition comprises the drug in an adhesive base.

25 Summary of the Invention

The present invention is based on the discovery that *l*-MPH may be used as an anticonvulsant, e.g. to treat patients suffering from epilepsy, or to treat bipolar disorder or narcolepsy, especially if delivered by a route
30 other than oral. According to a second aspect of the invention, a topical composition comprises *l*-MPH and a suitable carrier.

It has surprisingly been found that the *l*-enantiomer possesses pharmacological activity broadly similar to that
35 of the *d*-enantiomer and the racemate. The two enantiomers and the racemate induced similar stimulant effects in the Irwin Observation Test, including mainly excitation with

signs of hypersensitivity to external stimulation, stereotypies with fore-paw treading, mydriasis and hyperthermia. Perhaps even more surprisingly for a stimulant, the l-enantiomer was found to possess anticonvulsant activity in an animal model, the Pentylentetrazole (PTZ) Seizure Test, a property which was not shown by the d-enantiomer.

In the Irwin profile, sedation was not noted at the doses of l-MPH used in the PTZ test. Slight signs of stimulation were noted at doses having anti-convulsant effects but they were only slightly more marked than those seen with doses equivalent to the therapeutic dose of the racemate on a mg/kg basis. l-MPH was also found to antagonise barbitol-induced sleep.

In addition, it has been found that, in the mouse, l-MPH was found not to be linked with liver damage as assessed by increased plasma level of alanine aminotransferase and microscopic examination for hepatic necrosis, and also that l-MPH had little or no effect on the activities of cytochrome P₄₅₀ sub-types 1A2, 2E1 and 3A4. At very high doses, some inhibition of cytochrome P₄₅₀ sub-types C8/9, 2C18/19 and 2D6 was found, but the concentrations required to inhibit enzyme activities (100 μ M) were much greater than the maximum concentrations likely to be found in vivo and are therefore not likely to be clinically relevant.

These findings indicate a low potential for l-MPH to be associated with side-effects on the liver, sedation or significant drug interactions. Further, the adoption of topical dosing, with the potential for cutting down dosing frequency and for continuing therapy during sleeping hours, may remove the problem of patient compliance associated with existing anti-epilepsy treatments.

Description of the Invention

As indicated above, the PTZ model has shown that l-MPH delivered subcutaneously has anticonvulsant potential. To overcome the pre-systemic metabolism of l-MPH which occurs

with oral administration and to counteract possible problems with compliance, 1-MPH may be delivered in a topical presentation.

Topical application of drugs provides many advantages over conventional oral administration. Advantages include convenience, uninterrupted therapy, improved patient compliance, ease of discontinuation, elimination of presystemic metabolism, a high degree of control over blood concentration of the drug and improved overall therapy.

10 The 1-MPH may be administered by the same means as is known for *d,l*-MPH, e.g. as described in WO-A-99/30694. In this way, substantially zero order kinetics, for delivery to the skin or mucosa, over a period of at least 10 hours, may be achieved.

15 The 1-MPH may also be administered by any other conventional topical application method at any anatomical site. Conventional dosing parameters may be adopted, i.e. those which are known to or adapted to the practice of those skilled in the art.

20 Known topical formulations comprise emulsions, suspensions, solutions, creams, ointments and many other, with or without a vehicle such as a subcutaneous implant, suppository, patch or applicator. The most appropriate formulation and its delivery will be apparent to, or can readily be determined by, one skilled in the art. Similarly, the appropriate dosage can be determined, having regards to conventional factors such as the condition of the patient, the severity of the illness, the number and type of applications, etc. A typical dosage might comprise
25 10 to 200 mg 1-MPH, to be applied 1-2 times per day.

30 The 1-MPH will usually be used in substantially single enantiomer form, e.g. in at least 90%, preferably at least 95%, and most preferably at least 98% ee, with respect to *d*-MPH. Methods for preparing the active component used in this invention are known.

35 The following Tables report the results of the Irwin, PTZ and barbital interaction (sleep induction) tests.

Description of these tests may be found in Psychopharmacologica, 13:222-257 (1968), Krall et al, Epilepsia 19:409-428 (1978), and Simon et al, J. Pharmacol, Paris 13:241-252 (1982). See also Roux et al, Phoenix
5 International Pharmacology Reports Nos. D30.2061/2 and D99.021/2.

More particularly, Table 1 shows results of the Irwin test in the rat (3 rats per group), when 1-MPH is administered by the subcutaneous route. At higher doses,
10 of 64, 128 and 256 mg/ml, all rats exhibited further characteristics including sedation, fore-paw treading, stereotypies (head movements) and decreased muscle tone. In Table 1, the following apply:

+ = slight; ++ = moderate

15 (X/N) indicates the number of rats showing the symptoms.

Observations were performed at 15, 30, 60, 120, 180 minutes and 24 hours after administration.

Hyperthermia and mydriasis were evaluated by
20 comparison of the mean scores obtained in treated and control animals.

Tables 2a and 2b shows the effects of 1-MPH, Ro 15-4513 (positive control, proconvulsant) and Diazepam (positive control, anticonvulsant) in the PTZ test, using
25 10 rats per group. Table 2a reports mean results based on animals showing the symptoms (minimum = 3 animals). Table 2b reports results observed during 60 minutes. In these Tables:

Student's t Test : NS = Not Significant; * = $p < 0.05$;
30 ** = $p < 0.01$; *** = $p < 0.001$

Fisher's Exact Test : No indication = Not Significant;
** = $p < 0.01$; *** = $p < 0.001$

Table 3 shows the results of the barbitol-interaction sleep induction test, again using 10 rats per group, for 1-MPH and also d-MPH, d,l-MPH and caffeine. In Table 3, the
35 following apply:

Student's t Test : NS = Not Significant; * = $p < 0.05$;
** = $p < 0.01$; *** = $p < 0.001$

Fisher's Exact Test : (number of rats sleeping)

No indication = Not Significant; + = $p < 0.05$; ++ = $p < 0.01$;
5 +++ = $p < 0.001$

(#): maximum = 6 hours after barbital injection (taken 50
minutes after barbital injection).

Table 1

Dose (mg/kg)				
2	4	8	16	32
No change	Mydriasis + at 30'	Excitation + (2/3) at 30' Stereotypies (sniffing) (1/3) at 30' Mydriasis + at 30'	Excitation + (2/3) 60' → 120' Stereotypies (sniffing) (3/3) 30' → 120' Stereotypies (head movements) (1/3) 60' → 120' Mydriasis + at 30'	Excitation + (3/3) 15' → 30' Stereotypies (sniffing) (3/3) 15' → 120' 1 Fear (3/3) 15' → 120' 1 Reactivity to touch (3/3) 15' → 30' Mydriasis (++ 15' → 120') (+ at 180') Hyperthermia + at 30' and 120'

Table 2a

l-threo-Methylphenidate (mg/kg) s.c. -30 min	LATENCY TO CLONIC CONVULSIONS (sec)			LATENCY TO TONIC CONVULSIONS (sec)			LATENCY TO DEATHS (sec)		
	mean \pm s.e.m.	t value	% change from control	mean \pm s.e.m.	t value	% change from control	mean \pm s.e.m.	t value	% change from control
0	546.0 \pm 71.7	-	-	1170.0 \pm 94.0	-	-	1302.0 \pm 87.1	-	-
8	756.0 \pm 105.0 NS	1.652	+38%	1443.0 \pm 198.2 NS	1.245	+23%	1566.1 \pm 199.9 NS	1.211	+20%
16	1086.7 \pm 213.6 *	2.506	+99%	1785.0 \pm 292.2 *	2.196	+53%	1757.1 \pm 209.8 *	2.248	+35%
32	1782.0 \pm 161.7 ***	6.989	+226%	3070.0 \pm 164.6 ***	9.779	+162%	3260.0 \pm 121.7 ***	11.232	+150%
RO 15-4513 2 mg/kg s.c. -30 min	345.0 \pm 59.4 *	2.160	-37%	681.0 \pm 102.6 **	3.514	-42%	837.0 \pm 116.7 **	3.194	-36%

Table 2b

<i>l</i> -threo-Methylphenidate (mg/kg) s.c. -30 min	NUMBER OF CLONIC CONVULSIONS		NUMBER OF TONIC CONVULSIONS		NUMBER OF DEATHS	
	number of rats	% antagonism	number of rats	% antagonism	number of rats	% antagonism
0	10	-	10	-	10	-
8	10	0%	10	0%	10	0%
16	9	10%	8	20%	7	30%
32	10	0%	3 ++	70%	3 ++	70%
RO 15-4513 2 mg/kg s.c. -30 min	10	0%	10	0%	10	0%
DIAZEPAM 4 mg/kg s.c. -30 min	0 +++	100%	0 +++	100%	0 +++	100%

Table 3

TREATMENT (mg/kg) s.c. -30 min	NUMBER OF RATS SLEEPING	SLEEP DURATION (#) (min)		
		mean \pm s.e.m.	t value	% change from control
0	10	62.2 \pm 12.4		
<i>l</i> -threo-Methylphenidate				
0.5	9	63.8 \pm 18.5 NS	0.072	+3%
2	4 +	9.5 \pm 6.4 **	3.777	-85%
4	6	4.3 \pm 2.3 ***	4.589	-93%
8	1 +++	13.3 \pm 13.3	2.688	-79%
<i>d</i> -threo-Methylphenidate				
0.25	6	10.5 \pm 5.3 **	3.830	-83%
0.5	8	21.6 \pm 13.5 *	2.218	-65%
1	3 ++	2.1 \pm 1.5 ***	4.810	-97%
2	0 +++	0.0 \pm 0.0 ***	5.012	-100%
<i>dl</i> -threo-Methylphenidate				
0.25	9	94.2 \pm 18.3 NS	1.445	+51%
0.5	8	50.2 \pm 16.2 NS	0.590	-19%
1	0 +++	0.0 \pm 0.0 ***	5.012	-100%
2	4 +	19.0 \pm 12.6	2.449	-70%
4	0 +++	0.0 \pm 0.0 ***	5.012	-100%
Caffeine 16 mg/kg s.c. -30 min	1 +++	0.5 \pm 0.5 ***	4.968	-99%

CLAIMS

1. Use of 1-threo-methylphenidate for the manufacture of a medicament for the therapy of a convulsant state, a bipolar disorder or narcolepsy.
- 5 2. Use according to claim 1, for the therapy of epilepsy.
3. Use according to claim 1, for the therapy of bipolar disorder.
4. Use according to claim 1, for the therapy of narcolepsy.
- 10 5. Use according to any preceding claim, wherein the medicament is adapted for topical administration.
6. A topical composition comprising substantially single enantiomer 1-threo-methylphenidate.